Breast Cancer: Geographic, Migrant and Time-Trend Patterns

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I have been asked to talk about the descriptive epidemiology of breast cancer, a task that leads off most breast cancer conferences, and that usually ends with the presentation of data that everybody has seen many times before. I hope that by the end of this presentation, I can convince you that there actually have been some changes in the traditional wisdom, even about such things as geographic patterns and time trends. These changes are based on recent studies, and they will hopefully allow us to interpret these descriptive clues to breast cancer cause more meaningfully.

One thing that has not changed is the dramatic international variation. There is still a fivefold to sixfold difference in risk internationally, with the highest rates seen in the United States and northern Europe, the lowest rates in Asia, and intermediate rates in southern Europe and Latin America (Figure 1). There are two sets of rates shown in Figure 1, those for 1970 and those for 1985. This figure also shows another feature of the disease, that the incidence has been increasing in all these countries, but at a differential rate, with the most dramatic difference being a doubling in the incidence rate in Japan compared with approximately a 20% rise in the US, which results in a narrowing of same of the international gaps.

Part and parcel of the interpretation of these clues from international differences has come from the patterns in migrant populations. It is here that some of the traditional wisdom has been changing most dramatically in recent years. The initial studies of Asian Americans in this country performed in the 1950s and 1960s commented on the apparent persistence of low rates among the first and second generation migrants from Japan; some investigators even concluded that perhaps a genetic factor was involved.[1] In fact, this view persisted for the next 20 years, despite some evidence to the contrary, with the emphasis being on the closeness of the rates among both the first and second generation to those in their homeland.[2]

These findings led to the traditional wisdom that migrants who have breast cancer do not change their risk, that the second generation changes their risk only slightly, and that it is not until the third generation that the rates begin to move toward the rates of whites. As it turns out, this traditional wisdom ap-

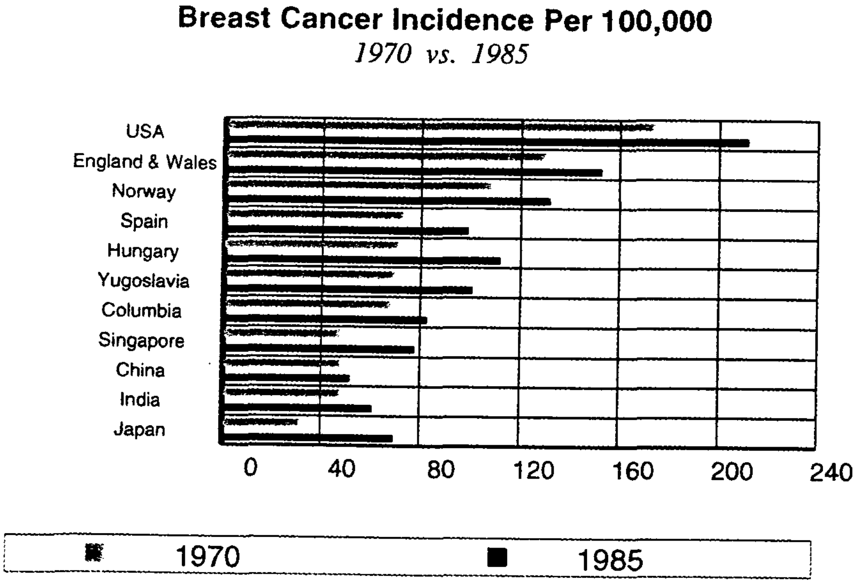

Figure 1. Age-adjusted breast cancer incidence rates for various countries for 1970 and 1985.

pears to be wrong. There were some suggestions that it was wrong from descriptive surveys performed in the 1980s,[3] but perhaps the most definitive quantification of the patterns among migrants came from a collaborative study led by Dr. Regina Ziegler. The study involved the Northern California Cancer Center, the University of Hawaii, and the University of Southern California, which included interviews with approximately 600 Asian American women who had breast cancer and more than 1,000 population-based controls.[4]

It was possible in this study to quantify the relative risks of breast cancer by migration status (Figure 2). The lowest risks occurred for Asian migrants from relatively rural areas in Asia, who had been in this country for less than a decade. The highest risk was seen for Asian American women who were born in this country and who had three to four grandparents also born in this country. This difference in relative risk between extremes translates to the approximately sixfold difference that is seen internationally between countries.

The changes in the traditional wisdom seen on this slide are twofold. One change relates to the risks in the migrating generation. Migrants themselves undergo a change in risk, incurring about an 80% increased risk after about 10 years of residence in this country. The second change is that Asian American women born in this country who were born to parents who were born in Asia experienced an additional increment in risk, which resulted in a substantially greater risk than would occur in their homeland.

Because this was a population-based study, we were able to calculate absolute rates of disease, which is useful to compare with outside rates. Although

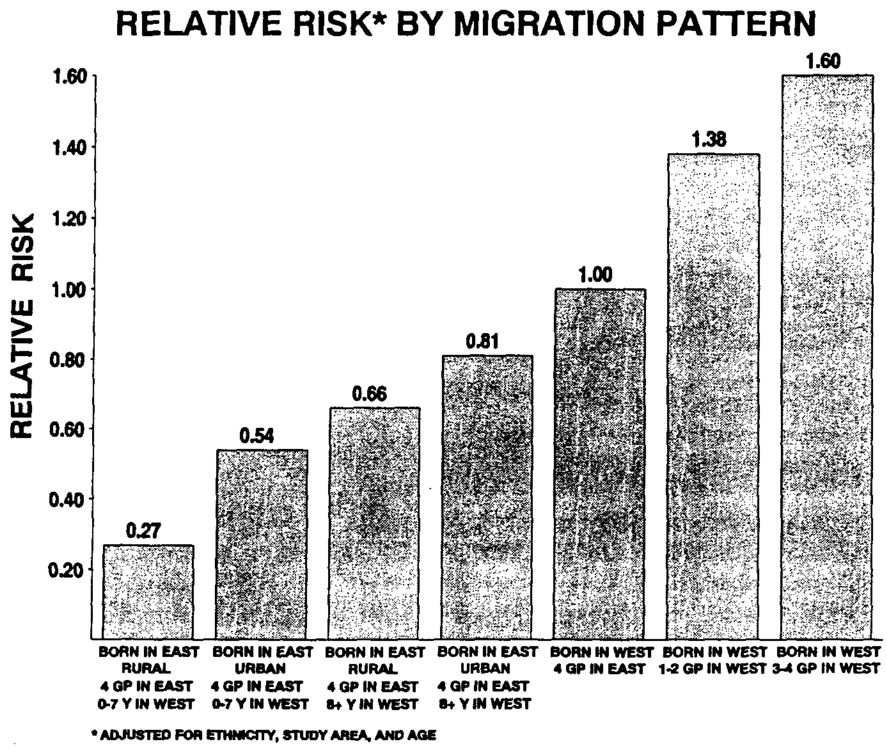

Figure 2. Relative risk* of breast cancer among Asian Americans by migration pattern adjusted for ethnicity, study area, and age. *Relative to 1.0 for women born in the West, with all 4 grandparents born in Asia. (GP = Grandparents; y = years living in the West)

this study included Japanese, Chinese, and Filipino Americans, the rates in Figure 3 are for Japanese Americans. The rate among migrants from urban areas in Japan is more than 80% greater than the rates reported from registries in urban areas of Japan. Women who were born in the U.S., but to parents who were born in Japan, experienced a rate essentially comparable to that for whites. Finally, Japanese American women who had grandparents born in the U.S., had rates that were actually in excess of the rates for whites.

There are several conclusions from these recent international and migrant studies:

1. The fivefold international differences still exist, but the gap is narrowing in some instances.
2. Recent Asian migrants experience risks similar to those experienced in their homeland, but after approximately a decade, their rates rise substantially.
3. Women who were born in the U.S. to migrant parents experience risks similar to those experienced by white women.

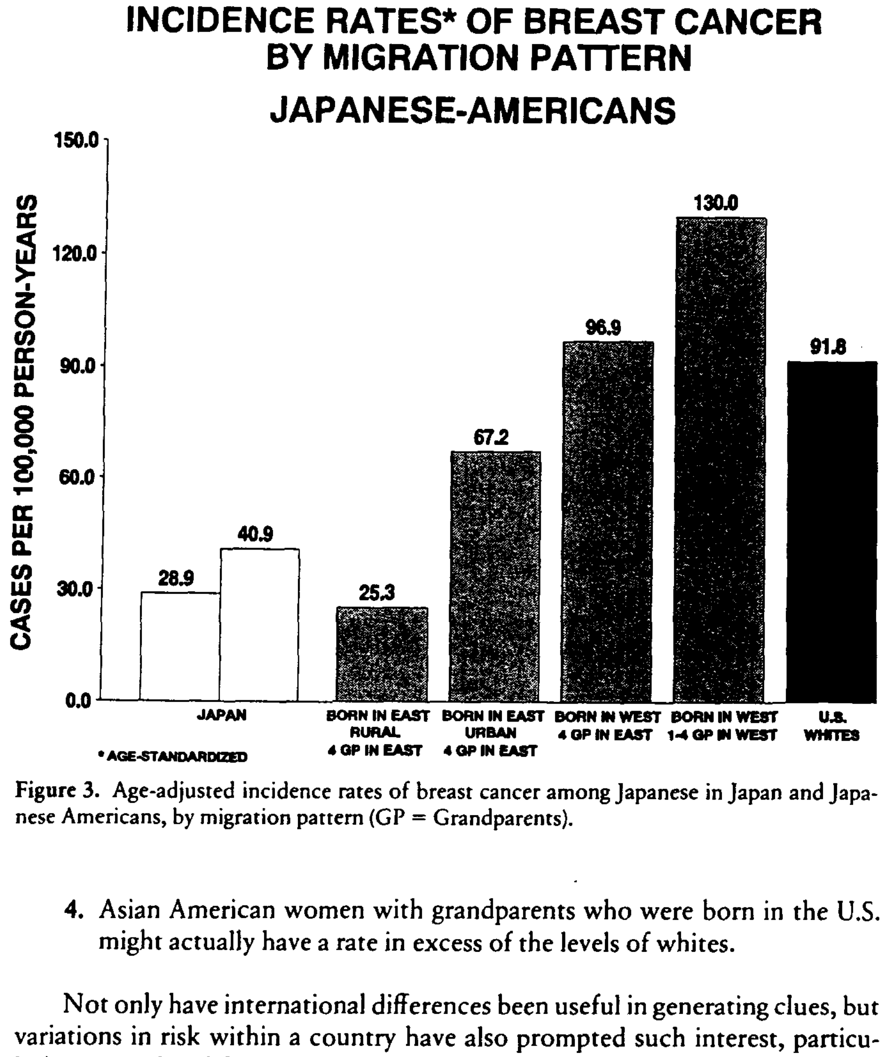

Figure 3. Age-adjusted incidence rates of breast cancer among Japanese in Japan and Japanese Americans, by migration pattern (GP = Grandparents).

4. Asian American women with grandparents who were born in the U.S. might actually have a rate in excess of the levels of whites.

Not only have international differences been useful in generating clues, but variations in risk within a country have also prompted such interest, particularly geographic differences seen in the U.S. Figure 4 is a map of breast cancer mortality by the state economic area. There are approximately 500 state economic areas in the United States. This map shows the recently well-publicized high breast cancer mortality rate in the Northeast, as well as the intermediate rates seen in the Midwest and far West, compared with low rates in the South. These data have been used extensively by some investigators to suggest that breast cancer may have a general environmental cause.

Initially, the speculation about general environmental causes related to natural constituents in the environment that might be protective. The two most prominently mentioned were selenium in the soil (and thus presumably in the diet) and sunlight-induced vitamin D production. Both of these factors occurred at a lower rate in the Northeast and at a higher rate in the South. More

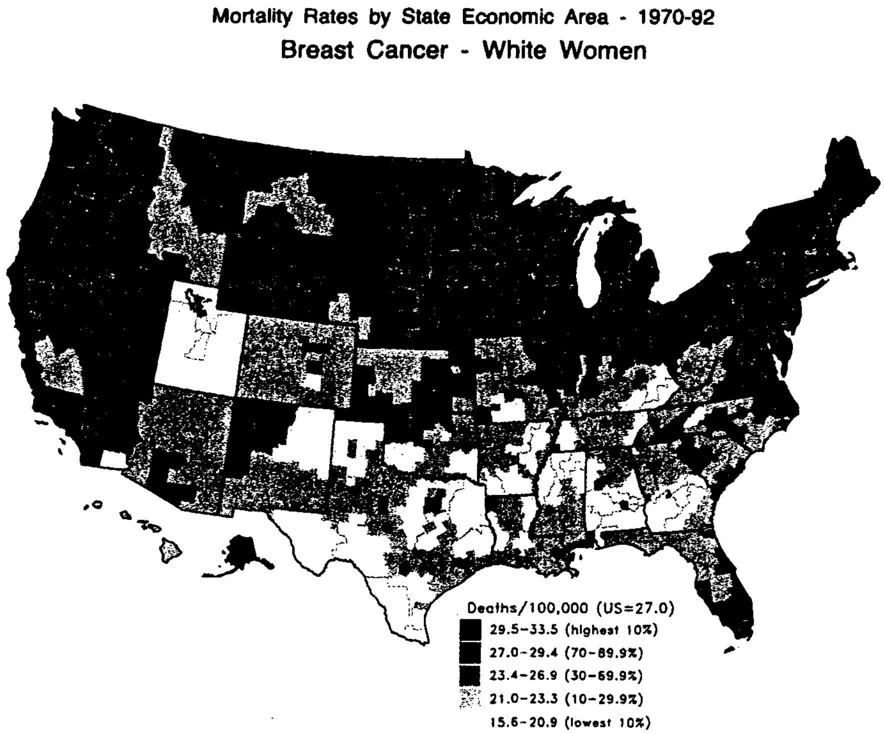

Figure 4. Age-adjusted breast cancer mortality rates for white women (1970–1992) by state economic area.

recent speculation has centered on potentially hazardous general environmental pollutants, including chlorophenothane (DDT), polychlorinated biphenyls (PCBs), electromagnetic radiation, and perhaps even vehicular emissions. Because little remains static in this country, particularly with respect to environmental exposures, assessment of time trends in these breast cancer mortality patterns should help in the assessment of the plausibility of some of those suggestions. To do this, one needs to shift to maps at the state level, to go back to time periods that do not have data available for the state economic area.

Figures 5 and 6 show state rates for 1940 and 1990. The geographic pattern has remained remarkably similar for 50 years, as has the overall rate. Perhaps noteworthy is that before 1940, DDT had not been introduced, PCBs were not widely used, and electromagnetic radiation as well as vehicular emissions were much less prevalent than they are currently.

In the search for general environmental causes, people have tended to overlook the possibility that some of this variability could be caused by regional differences in demographic and reproductive risk factors in the populations involved. This situation remained difficult to assess until recently. In 1987, the National Center for Health Statistics did a survey that allowed quantification

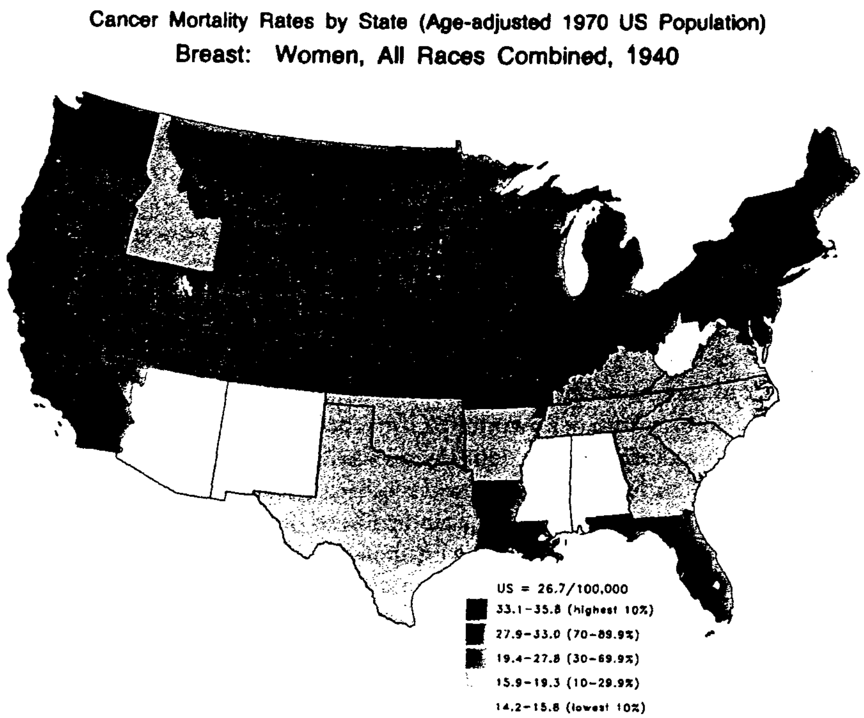

Figure 5. Age-adjusted breast cancer mortality rates for women (all races) by state in 1940.

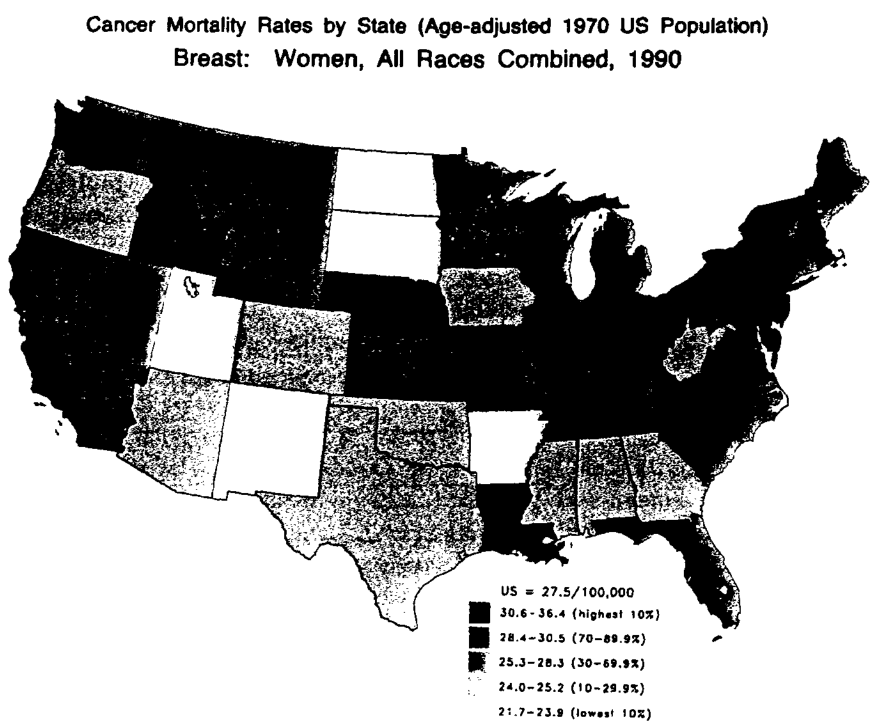

Figure 6. Age-adjusted breast cancer mortality rates for women (all races) by state in 1990.

of at least some breast cancer risk factors at a regional level. Dr. Susan Sturgeon took the lead in an analysis of these data to deduct the amount of variation that could be explained on the basis of these variables.[5] The variability is most prominent for women who are older than 50 years old. Table 1 presents relative risks for this age group in various regions compared with the risk in the South. Relative risks are presented unadjusted and then adjusted for the prevalence of various breast cancer risk factors. In the table the unadjusted relative risks show approximately a 30% excess in the mortality rate in the Northeast compared with the South, with the excess risks in the West and Midwest approximately half of that rate. Age alone does not account for any of this difference. Controlling for first birth, a powerful breast cancer risk factor, does result in a change, which reduces the apparent excess in the Northeast. The full model that was available allowed us to add seven other risk factors (along with age at first birth) and resulted in a different picture from the unadjusted model. The South still has a low risk compared with the rest of the country, but now the other regions look similar to each other, and display approximately a 10% excess risk compared with the rate in the South. Correspondingly, the initial 30% excess noted in the Northeast has been reduced to 13%. Given the crudeness and the limited nature of these data, it is actually still possible that the residual regional differences could also be explained on the basis of established breast cancer risk factors.

In summary, there are substantial regional differences in breast cancer mortality within the U.S. However, much of the variability can be explained by concomitant geographic variation in established risk factors. If the residual differences are caused by previously unrecognized environmental factors, they are likely to be factors that have been present for a very long time.

The final descriptive topic I am going to discuss relates to time trends in breast cancer, which have also been fairly provocative. There is an anomaly in the time-trend data, i.e., the mortality rates for breast cancer have remained virtually unchanged for 50 years, whereas incidence rates have risen substan-

Table 1 Relative Risk of Breast Cancer Mortality by Region in White Women Aged 50–79 Before and After Adjustment for Recognized Breast Cancer Risk Factors

	Region			
Risk Factor	*South*	*West*	*Midwest*	*Northeast*
Unadjusted	1.0	1.14	1.18	1.31
Age alone	1.0	1.15	1.18	1.30
Age, age at first live birth	1.0	1.13	1.13	1.19
Age, age at first live birth, and 7 other risk factors	1.0	1.13	1.08	1.13

tially. As noted in Figure 5, the age-adjusted mortality rate in 1940 was 26.7 per 100,000/y. The corresponding rate for 1990 was 27.5, or approximately a 3% increase during a 50-year period. Actually, there were some age-specific changes during this time period, primarily a slight rise at older ages, and a decrease at younger ages that tended to cancel each other out in the total. However, this is dramatically different form the incidence data, which has been increasing virtually in every place where there are reliable incidence registries for as long as these registries have been in existence.

Data from the National Cancer Surveys are illustrative. From the early 1950s to mid 1980s, there was very consistent and insidious rise of about 1%–2% per year in incidence that was more prominent in older women, and largely absent in younger women.[6] There was a much steeper increase in rates from the mid 1980s to the 1990s; there is substantial evidence that mammographic screening was primarily responsible for the increase. There has been some speculation that some of the earlier increases might also be ascribed to screening.

To assess this latter possibility, we were able to evaluate time trends in the Kaiser Permanente prepaid health plan in Portland, OR in collaboration with Dr. Andrew Glass.[7] The changes in rates during a time frame in that plan were the same as in the national surveys, a fairly consistent increase in older women, with little change in younger women. A unique aspect of this plan is that we could review medical records to determine how these tumors were diagnosed. Until the late 1970s, no tumors were diagnosed by mammographic screening. Thus, no part of the increase up through this time could be ascribed to mammographic screening. About one third of the increase from the late 1970s to the early 1980s appeared to be attributable to mammography, and the rest could not.

An additional unique opportunity in this plan, since it had been a member of the National Surgical Adjuvant Breast Program since its inception, was the fact that estrogen receptor assays were performed on virtually all breast cancer cases from the mid 1970s onward. Thus, we were able to look at time trends by receptor status (Figures 7 and 8). One can see that rates were increased for estrogen receptor positive disease fairly dramatically for both small and larger tumors. On the other hand, there was very little going on with respect to trends for estrogen receptor negative disease, either in the time period when mammographic screening was not a major factor, or in that time period when it was.

In summary, time trends in breast cancer incidence show a gradual and consistent increase from the 1950s to the mid 1980s. Little of this increase could be attributed to mammographic screening. Data from late in the period suggest that the increase might have been predominantly for estrogen-receptor positive disease. A comparable pattern is not seen for breast cancer mortality. Thus, it appears that if these patterns are not caused by some sort of artifact of ascertainment, then there is an increase in a version of breast cancer that is quite a bit less aggressive than the traditional disease, as indicated by the differential rise by estrogen receptor status, and by not showing up as an increase in mortality rates.

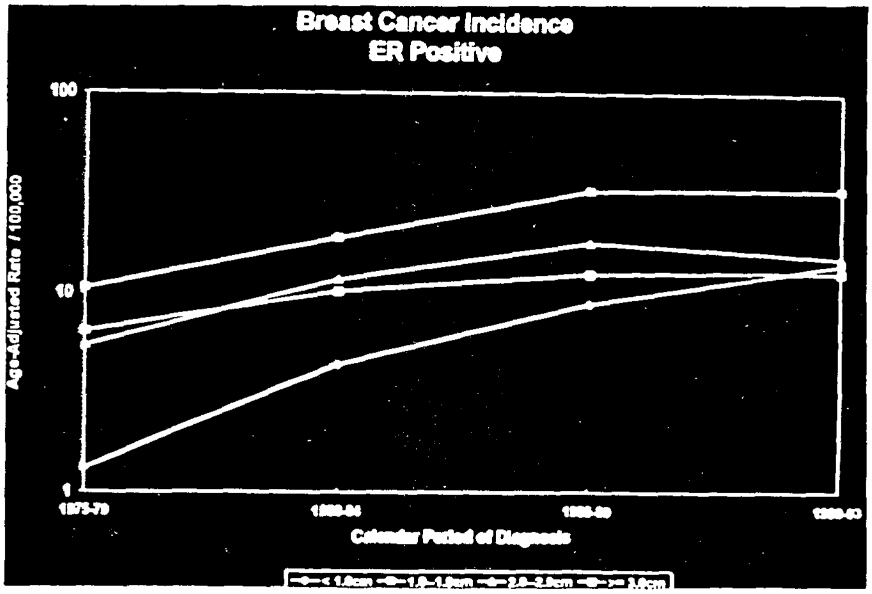

Figure 7. Age-adjusted, estrogen-receptor positive breast cancer incidence rates by time period in the Portland, OR, Kaiser Permanente Health Plan.

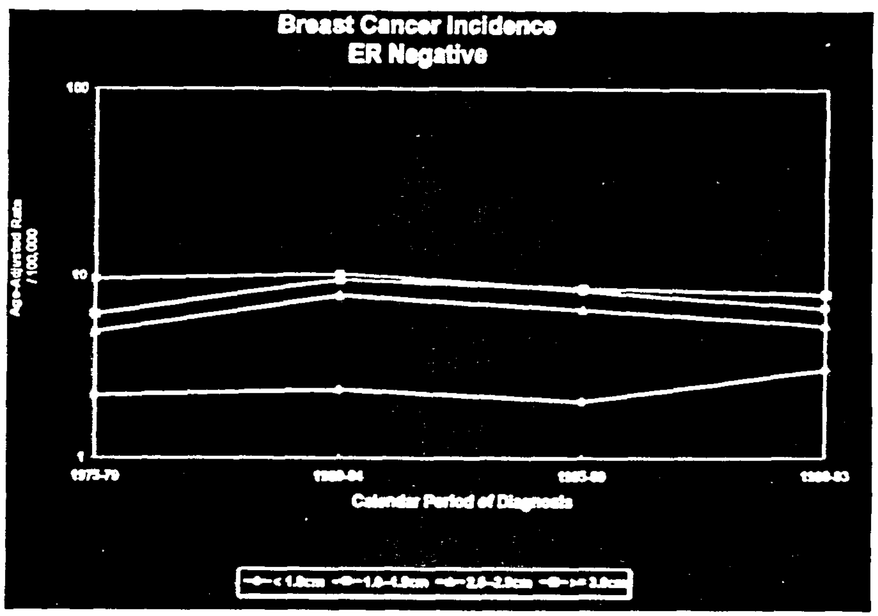

Figure 8. Age-adjusted, estrogen-receptor negative breast cancer incidence rates by time period in the Portland, OR, Kaiser Permanente Health Plan.

Underlying trends in breast cancer incidence from the mid 1980s to the current time remain largely unknown, which is indeed unfortunate. There has been a dramatic increase in the overall rate, a substantial but currently unknown portion of which is an artifact resulting from mammographic screening activities. It will be an important research goal of the epidemiology community to try and devise a way of assessing from now on the amount of time trends that are real and biologic, and how much of them are owing to screening or other types of interventions.

In summary, recently there have been dramatic changes in our perceptions of international migrant, and time-trend patterns in breast cancer risks based on new data generated in the past decade. Hopefully, these new insights will help us decipher the underlying biologic explanations of the descriptive epidemiology of this disease. Clearly, these are major clues to the cause of breast cancer, if we are only bright enough to decipher their meaning.

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